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10/509,141	09/27/2004	Reddy Bandi Parthasaradhi	H1089/20013	1984

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EXAMINER	
SHIAO, REI TSANG	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,141	PARTHASARADHI ET AL.	
	Examiner	Art Unit	
	Rei-tsang Shiao, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *12-18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/03/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending in the application.

Information Disclosure Statement

2. Applicant's Information Disclosure Statement, filed on February 03, 2005 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Responses to Election/Restriction

3. Applicant's election with traverse of Group I claims 1-11 and 19, in the reply filed on March 07, 2007, is acknowledged. The traversal is on the ground(s) that the special technical feature which links the claimed inventions is the structure of the compounds which is not taught by US Patent No. 5,196,444. This is found not persuasive, and the reasons are given *infra*.

Claims 1-20 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 1-11 and 19 are drawn to drawn to a crystalline Form III of a compound/composition of cilexetil 1,4-dioxane, and their processes of making.

The claims 1-20 herein lack unity of invention under PCT rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art, see Naka et al. US 5,196,444. Naka et al. disclose a similar catalyst compound of

candesartan cilexetil solvate (i.e., ethanol), see Working example 7 of columns 7-8. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

Furthermore, even if unity of invention under 37 CFR 1.475(a) is not lacking, which it is lacking, under 37 CFR 1.475(b) a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations:

> (1) A product and a process specially adapted for the manufacture of said product', or
>
> (2) A product and a process of use of said product; or
>
> (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
>
> (4) A process and an apparatus or means specifically designed for carrying out the said process; or
>
> (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

And, according to 37 CFR 1.475(c)

> if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b), unity of invention might not be present.

However, it is noted that unity of invention is considered lacking under 37 CFR 1.475(a) and (b). Therefore, since the claims are drawn to more than a product, and according to 37 CFR 1.475 (e)

> the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The claims lack unity of invention and should be limited to only a product, or a process for the preparation, or a use of the said product. In the instant case, Groups I-

II are drawn to various products, processes of making, and the final products do not contain a common technical feature or structure, and do not define a contribution over the prior art, i.e., a crystalline form III of claims 1-11 and 19, and a crystalline form IV of claims 12-18 and 20. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner. Claims 1-11 and 19 are prosecuted in the case. Claims 12-18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-4 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 9, line 2, respectively recites the limitation "figure 1" or "figure 2", fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims must stand alone to define invention, and incorporation into claims by express reference to specification is not permitted, are properly rejected under 35 U.S.C. 112, second paragraph, see Ex parte Fressola, No. 93-0828. Incorporation of the X-ray powder diffraction data into claims 4 and 9

respectively, would obviate the rejection.

Claims 3 and 8 respectively recite a X-ray powder diffraction pattern data. However, it is unclear what is the difference of the compound candesartan cilexetil 1,4 – dioxane solvate of claim 3 and 8. Are they the same candesartan cilexetil 1,4 –dioxane solvate compound? Clarification is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is well recognized in the art that process of preparing pharmaceutical composition will produce the thermodynamically stable form of crystals, thus, the instant Form III, after mixing, grinding, compressing would be transformed into a thermodynamically stable form(s), see Brittain's publication, pages 348-361.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention is a pharmaceutical composition comprising a crystalline form III of candesartan cilexetil 1,4 –dioxane solvate.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that a similar pharmaceutical composition comprising another crystalline forms of the compound candesartan cilexetil 1,4 –dioxane solvate. see Naka et al. US 5,196,444, columns 7-8 and 10.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the general description of the instant pharmaceutical composition on pages 3-4. There is no data present in the instant specification for the instant solid pharmaceutical composition,

wherein the crystalline form III still exists after the process of preparation, i.e., mixing, grinding, and compressing.

The breadth of the claims

The instant breadth of the rejected claims lack enablement requirement, specifically, the instant solid pharmaceutical composition comprises the crystalline form III after processes of preparing pharmaceutical compositions.

The quantity or experimentation needed and the level of skill in the art

While the level of the skill in the chemical arts is high, it would require undue experimentation of one of ordinary skill in the art to resolve any solid pharmaceutical compositions, wherein the crystalline form III still exist after the processes of pharmaceutical preparation. There is no data present in the instant specification for the instant solid pharmaceutical compositions, wherein the crystalline form III still exist after the process of preparation, i.e., mixing, grinding, and compressing. Therefore, the claims lack enablement for the pharmaceutical composition comprising the crystalline form III.

Prior Art Rejections

6. In regards to applicants compound claims 1-11 and 19, the prior art references of Naka et al. US 5,196,444, while not providing applicants' instant X-ray diffraction data. However, Naka et al. do name crystalline form of candesartan cilexetil solvate (i.e., 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-

yl]methyl]benzimidazole-7-car boxylate or its solvate or solvent form), see working example 7 of columns 7-8 and 10, which puts this product in the public domain. As these forms differ from the claims in that the references are silent on the X-ray diffraction data or the crystalline form, applicants must show that their crystalline form really is different from any of the ones prepared in the prior art. MPEP 2112 states: "Something which is old does not become patentable upon the discovery of a new property. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In this case, the 'unknown property" is the particular crystalline form. This is unknown because the references are silent on this property. MPEP 2112 goes on to state: "A rejection under 35 USC 102/103 can be made when the prior art product seems to be identical except that the prior art is silent as to an inherent characteristic. Where applicant claims a composition in terms of a function, property or characteristic and the compositions of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 USC 102 and 103, expressed as a 102/103 rejection." Again, the "characteristic" which the prior art is silent on is the crystalline form or the X-ray diffraction data.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. Se also Ex parte Anderson, 21 USPQ 2nd 1241 and 1251, discussion of

Rejection E. There, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior ad product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253). The "properties' branch of that statement applies here. Applicants are reminded that the PTO has no testing facilities. The composition of claim 19 is rejected under 35 USC 102(b) as the prior art references disclose compositions comprising applicants' instantly claimed invention as it is the state of the prior art that the preparation of pharmaceutical compositions requires, milling, adding excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms, see Brittain's publication, polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Science; 1999, V. 95, pages 348-361.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Naka et al. US 5,196,444.

Applicants claim a pharmaceutical composition comprising candesartan cilexetil 1,4 –dioxane solvate compound, see claim 19.

Naka et al. discloses a pharmaceutical composition comprising a compound candesartan cilexetil and a pharmaceutical acceptable diluent (i.e., solvent 1,4 –dioxane) or carrier (i.e., aqueous solution), see column 10, lines 54-60. It is noted that an acceptable carrier can be water and therefore the instant crystal forms of the instant compound dissolves in the composition (i.e., aqueous solution), and it will exist in free form and not as a crystal form or a solvate form. Therefore, the instant pharmaceutical composition is anticipated by Naka et al.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naka et al. US 5,196,444 in view of Brittain's publication, polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Science; 1999, V. 95, pages 348-361.

Applicants claim a candesartan cilexetil 1,4 –dioxane solvate compound and its pharmarceutical composition, and their processes of making, see claim 1, 5 and 19.

Determination of the scope and content of the prior art (MPEP §2141.01)

Naka et al. disclose a crystalline form of candesartan cilexetil 1,4 –dioxane solvate (i.e., 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate.solvate or its solvent form), and its

pharmaceutical composition, see working example 7 of columns 7-8 and 10.

Determination of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and Naka et al. is that Naka et al. is silent on the X-ray diffraction data of the instant compound.

Moreover, it is well recognized in the art that process of preparing pharmaceutical composition will produce the thermodynamically stable form of crystals, thus, Naka et al. crystal form and the instant form III after mixing, grinding, compressing would both be transformed into the same thermodynamically stable form(s) of the instant claimed form III, see Brittain's publication, pages 348-361.

Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art would find the instant claims 1-11 and 19 prima facie obvious **because** one would be motivated to employ the compounds/ compositions of Naka et al. to obtain the instant crystalline form of the same compound candesartan cilexetil or its solvate or solvent form and its pharmaceutical compositions, wherein the instant compound is in a crystalline form (i.e., form III). Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art, see In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties in terms of mechanic

benefits, the instant claimed crystalline forms and its compositions of known compounds would have been suggested to one skilled in the art.

The motivation to obtain the claimed crystalline form of the compound candesartan cilexetil or its pharmaceutical composition derives from known Naka et al. pharmaceutically useful compounds/compositions with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc., would possess similar activities (i.e., agents treating hypertension) to that which is claimed in the reference.

Claim Objections

10. Claims 1-6 and 19 are objected to as depending on a non-elected subjected matter (i.e., amorphous form or form IV of claims 1-6). It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on pages 2-3 *supra*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rei-tsang Shiao, Ph.D.
Patent Examiner
Art Unit 1626

April 16, 2007